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Maurice-Stam, H.; Oort, F.J.; Last, B.F.; Grootenhuis, M.A.

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# A predictive model of health-related quality of life in young adult survivors of childhood cancer

H. MAURICE-STAM, PHD, *Pediatric Psychosocial Department, Emma Children's Hospital, Academic Medical Center, University of Amsterdam*, F.J. OORT, PHD, *Department of Medical Psychology, Academic Medical Center, University of Amsterdam, and Department of Education, Faculty of Social and Behavioural Sciences, University of Amsterdam*, B.F. LAST, PHD, *Pediatric Psychosocial Department, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, and Department of Developmental Psychology, Vrije Universiteit Amsterdam*, & M.A. GROOTENHUIS, PHD, *Pediatric Psychosocial Department, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, the Netherlands*

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**A predictive model of health-related quality of life in young adult survivors of childhood cancer**

This study aimed to examine factors that affect survivors' health-related quality of life (HRQoL), using a theoretical model in which demographic and medical characteristics explain HRQoL mediated by course of life, coping and social support. In a cross-sectional design, 353 survivors aged 18–30 years completed questionnaires. Structural equation modelling was performed to investigate the relationships among the variables in the model and to test whether the model fitted the data. The model fitted the data closely: $\chi^2(14) = 21.61$, $P = 0.087$; root mean square error of approximation = 0.039, 90% confidence interval [0.00; 0.070]. The effect of medical and demographic characteristics on HRQoL was mediated by coping. Survivors having been treated with both chemotherapy and radiotherapy were most at risk for worse HRQoL because they suffer more from current health complaints and were less inclined to predictive and active coping. Screening survivors medically as well as psychosocially could help to identify patients with the greatest needs and direct interventions by which the follow-up care could be improved.

*Keywords:* neoplasm in childhood, long-term survivors, quality of life, psychological adaptation.

## INTRODUCTION

The introduction of the modern therapies has resulted in an enormous increase of survival in childhood cancer. Nowadays, overall, the 5-year survival was more than 70% among children diagnosed with cancer in Europe, compared with 30% in the 1960s (Novakovic 1994; Stiller & Draper 1998; 2005; Magnani *et al*. 2006; Sankila *et al*. 2006). Approximately two young adults from every 1000 ever suffered from childhood cancer in the Netherlands (Paulides *et al.* 2000). The enormous increase in the number of survivors of childhood cancer reaching adulthood over the last decades has heightened the need to investigate the consequences of both the disease and its treatment. An increasing number of studies has been directed at assessing health-related quality of life (HRQOL), as an indicator of adjustment to the consequences of childhood cancer. Many survivors appeared to experience good HRQoL, but some were more vulnerable to maladjustment than others (Stam *et al.* 2001; Langeveld

Correspondence address: Heleen Maurice-Stam, Pediatric Psychosocial Department EKZ AMC, G8-224, Meibergdreef 9, NL-1105 AZ Amsterdam, the Netherlands (e-mail: h.stam@amc.uva.nl).

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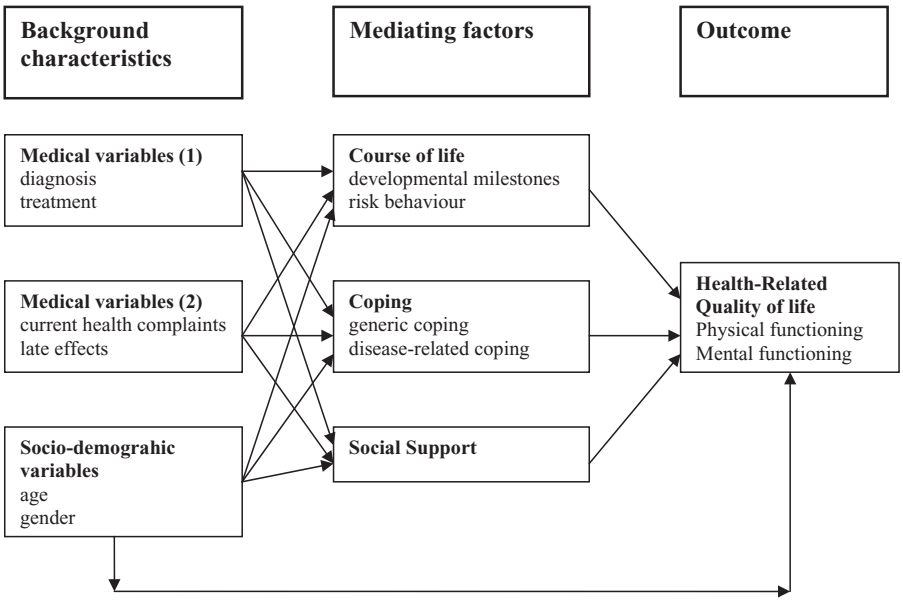


**Figure 1.** Conceptual model of the process of adjustment to childhood cancer: background characteristics affecting health-related quality of life via course of life, coping and social support.

*et al*. 2002; Eiser 2004). It is therefore important to draw insight into the process of adjustment and to identify factors that predict better or worse HRQoL.

The impact of demographic and medical variables on survivors' HRQoL has been discussed to some extent in many studies of HRQoL (see review of Langeveld *et al*. 2002). An increased risk of worse HRQoL was found to be associated with female gender, older age at follow-up, a greater number of relapses, the presence of severe functional impairment and cranial irradiation. In addition, survivors of central nervous system tumours and subsets of survivors of acute lymphatic leukaemia seemed to be at risk for educational deficits; the same is true for cranial irradiation and early age at diagnosis. However, the demographic and medical variables only explain variations in HRQoL to a limited extent (Langeveld *et al.* 2002; Zebrack & Chesler 2002; Zebrack *et al*. 2002, 2004, 2004b; Stam *et al.* 2006). Insight into the psychosocial variables that predict HRQoL is important, as this could be helpful in directing interventions for survivors of childhood cancer. Previous studies indicated that, among others, coping (Phipps & Srivastava 1997; Phipps *et al*. 2006; Stam *et al.* 2006), social support (Fritz *et al.* 1988; Sloper *et al.* 1994; Kazak *et al*. 1997; Kazak 1998) and the achievement of developmental milestones while growing up with a history of cancer (Stam *et al.* 2005; Schwartz & Drotar 2006; Maurice-Stam *et al*. 2007) are related to survivors' HRQoL.

Equivalent to other conceptual frameworks used to explain adjustment in paediatric patients (Wallander & Varni 1998) and adult patients (Wilson & Cleary 1995), adjustment in survivors of childhood cancer (operationalized as HRQoL) is presumed to be an outcome of a process over time that is influenced by demographic and medical variables mediated by psychosocial variables. In other words, demographic and medical variables affect HRQoL directly as well as indirectly through psychosocial variables, such as course of life, coping and social support. The present study is especially directed at the psychosocial factors because these play an important role in (paediatric) psychology and are assumed to be susceptible to change. Our assumptions about the process of adjustment to cancer are reflected in the conceptual model (Fig. 1). Several parts of the model have been investigated separately (Fritz *et al.* 1988; Sloper *et al.* 1994; Phipps & Srivastava 1997; Kazak *et al.* 1997; Kazak 1998; Langeveld *et al.* 2002, 2004b; Stam *et al.* 2005, 2006; Phipps *et al.* 2006; Schwartz & Drotar 2006), but to date, the entire model has not yet been tested. The aim of the present study was to examine the entire model, including direct and indirect effects, in order to test whether the theoretical and conceptual model fitted the process of adjustment to childhood cancer. Structural equation modelling (SEM) was used to test the conceptual model because, in contrast to traditional analytical procedures as linear regression analysis, SEM makes it possible to distinguish between direct and indirect effects and provides information on the degree of fit for the entire model. The extent to which several demographic and medical variables explained HRQoL in young adult survivors of childhood cancer mediated by course of life, coping and social support was examined. The results could demonstrate the importance of interpreting HRQoL as outcome based on both medical and psychosocial factors. Subsequently, this could be helpful in tracing survivors at risk of worse HRQoL and in

developing interventions for survivors of childhood cancer, by which the follow-up care could be improved.

## METHODS

### Procedure

In 2001 and 2002, survivors of childhood cancer aged between 18 and 30 years who attended the long-term follow-up clinic at The Emma Children's Hospital/ Academic Medical Center in Amsterdam, were invited (in person by a psychologist) to fill in several questionnaires anonymously. After completing the questionnaires at home, they were requested to return them in a stamped addressed return envelope. A reminder letter was sent with a copy of the same questionnaires after a month. The inclusion criteria were (1) age at study 18–30 years; (2) end of successful treatment at least 5 years before; (3) age at cancer diagnosis <18 years; and (4) ability to understand Dutch questionnaires.

A unique patient number made it possible to gather medical information from the respondents as well as from the non-respondents. The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam.

### Measures

#### *Background characteristics*

Medical data concerning diagnosis, treatment and late effects were obtained from the registry of the long-term follow-up clinic at The Emma Children's Hospital/ Academic Medical Center in Amsterdam. The registry is based on the medical information the oncologist receives at the annual evaluation; the oncologist also annotated whether the patient reported psychosocial or cognitive problems. The late effects were categorized into 10 groups, based on Stevens *et al.* (1998), i.e. endocrine, organ toxicity, mobility/orthopaedic, infertility, sensory, cosmetic, fatigue, subsequent neoplasm, psychosocial/cognitive and neurological. These health problems are clustered into two dichotomous variables: 'physical late effects' (yes/no) and 'psychosocial and/or cognitive and/or neurological late effects' (yes/no). Apart from the registration at the long-term follow-up clinic, all respondents were asked to fill in whether they had experienced health complaints in the last 4 weeks (yes/no).

#### *Mediating factors*

Course of life, generic coping, disease-related coping and social support were the mediating factors in the present study.

Course of life was measured with the 'course of life' questionnaire (Grootenhuis *et al*. 2003; Stam *et al.* 2005), which assesses the achievement of developmental milestones. The items concern behaviour characteristic of certain age stages, developmental tasks and the limitations children might face when they grow up with a chronic or life-threatening disease. The respondents are asked retrospectively whether they have achieved certain milestones or at what age they achieved the milestones. The answers are dichotomized, if necessary, before being added up to the scale score. The items are divided into five scales: autonomy development (six items, autonomy at home and outside the home); psychosexual development (four items, love and sexual relations); social development (12 items, contacts with peers); antisocial behaviour (four items, misbehaviour at school and outside school);and substance use and gambling (12 items). A higher score on the scales indicates the accomplishment of more developmental milestones or the displaying of more antisocial behaviour and more substance use and gambling. For the complete description of the scale-items please refer to Stam *et al.* (2005). The validity of the course-of-life scales is satisfactory (Grootenhuis *et al.* 2003; Stam *et al.* 2005). The test–retest reliability is good (Last *et al*. 2000) and the internal consistency is moderate to good (Grootenhuis *et al.* 2003).

For reasons of parsimony, the five scales were aggregated into two summary scales: developmental milestones and risk behaviour. The relative contribution of each scale to the summary scales was derived from principal components analysis (PCA), oblique rotation (Oblimin).

Generic coping was measured with the Utrecht Coping List (UCL), a questionnaire about coping with stressful or problematic situations (Schreurs *et al*. 1993). It consists of 47 questions with answers on a Likert scale. The UCL covers seven coping styles: active problem-focusing, palliative reaction pattern, avoidance behaviour, seeking social support, passive reaction pattern, expression of emotions and comforting emotions. A higher scale score means more use of the coping style. The internal consistency and validity is satisfactory (Oldehinkel *et al*. 1992; Schreurs *et al.* 1993).

For reasons of parsimony, the seven scales were aggregated into three summary scales: passive coping, active coping and sharing emotions. The relative contribution of each scale to the summary scales was derived from PCA, Oblimin.

Disease-related cognitive coping was assessed using the cognitive control strategies scale (CCSS). The instrument, based on the model of Rothbaum *et al.* (1982), assesses on a Likert scale to what extent respondents try to gain sense

of control over the illness by using cognitive coping strategies. The items of the CCSS were grouped into three scales: predictive control (being optimistic about the course of the disease); vicarious control (attributing power to medical caregivers and treatment); and interpretative control (searching for information in order to better understand emotional reactions and to gain insight into the situation). Higher scores represent a stronger reliance upon the control strategy. The internal consistency is satisfactory and the questionnaire proved to be useful in earlier studies (Grootenhuis *et al*. 1996; Grootenhuis & Last 2001; Loonen *et al*. 2002; Houtzager *et al*. 2004).

The amount of social support the respondents indicate that they received from their social networks was assessed with the Social Support Questionnaire for Transactions (SSQT) developed by Suurmeijer *et al*. (1995), Doeglas *et al*. (1996) and van Sonderen (2004). This questionnaire measures the frequency of 41 actual supportive transactions on a Likert scale. The supportive transactions are categorized into seven subscales, and a total score is calculated by adding up the item scores: the more supportive transactions, the higher the scores. The psychometric properties of the SSQT have proved to be good (Doeglas *et al.* 1996; van Sonderen 2004). The SSQT total score was used in the present study.

*Outcome*

Health-related quality of life was assessed with the RAND-36, the Dutch version of the Medical Outcomes Study Short-Form General Health Survey (MOS-SF-36) and almost identical to the Dutch SF-36 (Aaronson *et al*. 1998). The RAND-36 is composed of 36 items with standardized response choices, clustered into eight multi-item scales: physical functioning; social functioning; role limitations due to physical health problems; role limitations due to emotional problems; general mental health; vitality; bodily pain; and general health perceptions. All raw scale scores are converted to a 0–100 scale, with higher scores indicating higher levels of functioning or well-being. The validity and reliability of the RAND scales are satisfactory (van der Zee & Sanderman 2003). Following the method of Ware & Kosinski (2001), we used PCA to aggregate the scale scores into two summary scales: mental component scale (MCS) and physical component scale (PCS). The relative contribution of each scale to MCS and PCS was derived from PCA, Oblimin.

### Statistical analyses

Missing values were handled according to the guidelines given in the manuals of the relevant questionnaires and, after that, through the expectation-maximization estimation method (SPSS 2002). A sample size of 353 remained available for analysis.

Structural equation modelling using LISREL 8.30 (Jöreskog & Sörbom 1996) was performed to investigate the relationships among the variables in the conceptual model and to test whether the conceptual model fitted the data. In SEM, the covariance structure that follows from the proposed model is fitted to the observed covariances (Jöreskog & Sörbom 1996). The maximum likelihood estimate method yields estimates of the regression coefficients in the model, standard errors and a $\chi^2$-test of overall goodness-of-fit (Bollen 1989). An alternative fit measure is the root mean square error of approximation (RMSEA). According to a generally accepted rule of thumb (Browne & Cudeck 1992), RMSEA values lower than 0.08 indicate satisfactory fit, and values lower than 0.05 indicate close fit. In addition to overall goodness-of-fit, component fit was evaluated by inspecting standardized discrepancies between observed and expected correlations, and LISREL's modification indices (Bollen 1989).

We used a significance level of $P < 0.05$ for the regression coefficients. Standardized regression coefficients of 0.1 were considered small, 0.3 medium and 0.5 large (Cohen 1988).

## RESULTS

### Survivors

A total of 499 young adult survivors (262 men and 237 women) were asked to take part in the Vragenlijsten kinder Oncologie Latere Gevolgen (VOLG) study. A total of 355 questionnaires were returned (response 71.0%), including two questionnaires that could not be used for analysis. Of the 144 survivors who did not complete the questionnaires 18 returned the non-response form. Most of these non-respondents reported that they did not have enough time or did not feel like taking part in the study ($n = 10$). Two survivors refused because they did not want to be confronted with cancer again. The remaining six did not complete the questionnaires for other reasons.

The data of 353 survivors could be used for analysis. Respondents were older than non-respondents at time of study and diagnosis, and there were a higher percentage of women among the participants than among the non-participants. No significant differences were found with regard to diagnosis and treatment, time since first diagnosis, time since end of last treatment, duration of treatment, relapse or second malignancy, and late effects as registered at the long-term follow-up clinic (Table 1).

**Table 1.** Characteristics of the survivors

| | Respondents ($n = 353$) | | | Non-respondents ($n = 146$) | | |
|---|---|---|---|---|---|---|
| | M | SD | Range | M | SD | Range |
| Age at study (years) | 24.3† | 4.0 | 17.7–31.1 | 23.2 | 3.9 | 18.0–30.8 |
| Age at first diagnosis (years) | 7.3* | 4.7 | 0.0–17.0 | 6.3 | 4.7 | 0.0–17.0 |
| Time since first diagnosis (years) | 17.0 | 6.0 | 6.2–30.7 | 16.8 | 5.5 | 5.4–28.4 |
| Time since end of last treatment (years) | 15.5 | 5.5 | 4.9–30.3 | 15.6 | 5.4 | 4.8–28.2 |
| Duration of treatment (months) | 12.5 | 10.5 | 0.0–72.5 | 10.8 | 11.5 | 0.0–71.0 |
| | | | *n* | % | *n* | % |
| Gender | | | | | | |
| Female | | | 178 | 50.4* | 59 | 40.4 |
| Male | | | 175 | 49.6 | 87 | 59.6 |
| Diagnosis | | | | | | |
| Leukaemia/lymphoma | | | 176 | 49.9 | 64 | 43.8 |
| Solid tumour | | | 152 | 43.1 | 77 | 52.7 |
| Brain tumour | | | 25 | 7.1 | 5 | 3.4 |
| Treatment | | | | | | |
| Chemotherapy (with/without surgery) | | | 199 | 56.4 | 79 | 54.5 |
| Radiotherapy (with/without surgery) | | | 14 | 4.0 | 8 | 5.5 |
| Surgery alone | | | 26 | 7.4 | 16 | 11.0 |
| Combination therapy (chemotherapy + radiotherapy, with/without surgery) | | | 114 | 32.3 | 42 | 29.0 |
| Late effects | | | | | | |
| No problems | | | 45 | 12.7 | 54 | 9.6 |
| Physical | | | 299 | 84.7 | 122 | 83.6 |
| Psychosocial/cognitive/neurological | | | 114 | 32.3 | 54 | 37.0 |
| Relapse or second malignancy | | | | | | |
| Yes | | | 43 | 12.2 | 18 | 12.3 |
| No | | | 310 | 87.8 | 128 | 87.7 |
| Parents' educational level‡ | | | | | | |
| Low | | | 137 | 41.1 | | |
| Middle | | | 98 | 29.4 | | |
| High | | | 98 | 29.4 | | |
| Native country | | | | | | |
| The Netherlands | | | 338 | 96.6 | | |
| Other | | | 12 | 3.4 | | |

*$P < 0.05$.
†$P < 0.01$.
‡Highest level of education completed: Low = primary education, technical and vocational training, lower and middle general secondary education; Middle = middle vocational education, higher general secondary education, pre-university education; High = higher vocational education, university.
M, mean; SD, standard deviation.

The study sample appeared to be representative of all 18 to 30-year-old survivors who attended the long-term follow-up clinic of the Academic Medical Centre in Amsterdam in 2001 and 2002, with the exception of the survivors suffering from serious cognitive sequelae of disease and treatment. These survivors were not represented because they were not able to fill in the questionnaires.

## Adjustment to childhood cancer

### *Model fit*

The conceptual model (Fig. 1) was fitted to the correlation matrix. The chi-square (CHISQ) measure of overall goodness-of-fit was 77.55 (CHISQ22, $P = 0.00$) and the hypotheses of exact fit was rejected. The RMSEA was 0.085 and the 90% confidence interval (CI) ranged from 0.065 to 0.11, which indicated that the fit was not quite satisfactory. Inspection of component fit indices indicated several possible modifications. First, the modification indices suggested direct effects of 'current health complaints', 'physical late effects' and 'psychosocial/cognitive/neurological late effects' on HRQoL, which suggested to consider these factors as 'mediating factors' instead of 'background characteristics'. Second, the modification indices suggested an additional direct effect of 'relapse/second tumour' on HRQoL. These modifications were added stepwise to the model, resulting in a modified model with close fit: CHISQ(14) = 21.61, $P = 0.087$; RMSEA = 0.039, 90% CI [0.00; 0.070]. The modified model explained 46% of the variance in MCS and 40% of the variance in PCS. Figure 2 gives a graphical

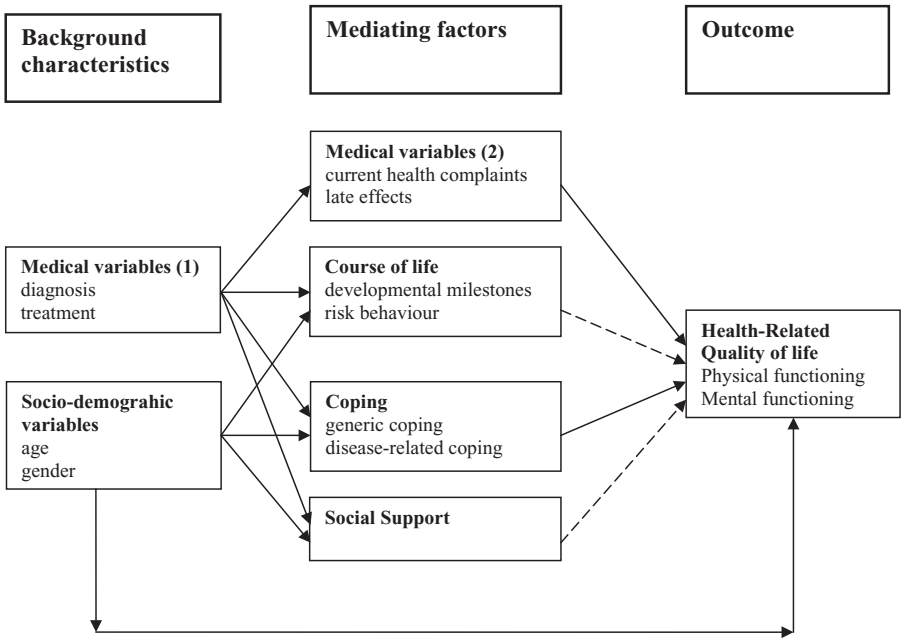


**Figure 2.** Modified final model of the process of adjustment to childhood cancer: background characteristics affecting health-related quality of life via medical variables, course of life, coping and social support. Non-significant paths (at 0.05) are marked with an interrupted arrow (– – –►).

display of the modified model, and Table 2 gives the parameter estimates.

The first part of Table 2 presents the effects of demographic and medical variables (background characteristics) on the mediating factors; the second part contains the direct effects of the background characteristics on HRQoL; and the third part contains the effects of the mediating factors on HRQoL. The total effect of a variable on HRQoL can be calculated using the direct and indirect pathways in the modified model, as the following example illustrates. Table 2 shows that 'brain tumour' has only indirect effects on HRQoL. First, the diagnosis 'brain tumour' compared with 'leukaemia/lymphoma' was associated with an increase of 0.17 standard deviation (SD) in 'psychosocial/cognitive/neurological late effects', and with a decrease of 0.13 SD in 'developmental milestones' and 'risk behaviour'. Second, it is shown that the effect of 'psychosocial/cognitive/neurological late effects' on HRQoL was –0.11 and –0.15 for MCS and PCS respectively. The significant (indirect) effects of 'brain tumour' on MCS and PCS can be calculated as follows: $0.17 \times -0.11 = -0.019$ and $0.17 \times -0.15 = -0.026$ respectively. Apart from that, the other indirect effects of 'brain tumour' on MCS and PCS were small and non-significant, so that the total effect remains small, –0.05 and –0.06 respectively.

*Effects of the background characteristics*

All significant regression coefficients of the demographic and medical variables were small to medium (Cohen 1988), ranging from $\beta = -0.13$ (brain tumour) to $\beta = -0.34$ (radiotherapy and chemotherapy). Treatment variables appeared to affect the mediating factors most strongly.

Direct as well as indirect effects of gender on HRQoL were found. Being female had a negative impact on HRQoL, directly as well as indirectly via 'current health complaints', 'interpretative control', 'predictive control', 'passive coping' and 'sharing emotions'.

Survivors of brain tumours had worse HRQoL than survivors of leukaemia/lymphoma, via 'psychosocial/cognitive/neurological late effects'. On the contrary, survivors of solid tumours reported better HRQoL via these late effects, but their HRQoL became worse via 'passive coping'. Survivors having been treated with chemotherapy with or without radiotherapy reported worse HRQoL than those treated with surgery only, mediated by 'current health complaints'. The negative effect of 'radiotherapy and chemotherapy' on HRQoL was also mediated by 'predictive control' and 'active coping'.

It is interesting that 'brain tumour', 'radiotherapy and chemotherapy' and 'radiotherapy' were associated with the achievement of fewer developmental milestones. Furthermore, 'female gender' and 'brain tumour' were associated with less risk behaviour. However, these mediating factors appeared not to affect HRQoL significantly.

Furthermore, 'age at first diagnosis' and 'duration of treatment' had a negative impact on HRQoL, mediated by 'passive coping'. Finally, a small direct negative effect of 'relapse/second tumour' on PCS was found.

**Table 2.** Predictive model of health-related quality of life (HRQoL) in young adult survivors of childhood cancer: standardized regression coefficients and percentage of explained variance of the modified model*

| | Age | Women | Brain tumour† | Solid tumour | Radio chemo therapy‡ | Radio therapy‡ | Chemo therapy‡ | Age at first diagnosis | Treatment duration | Relapse second tumour |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 Effects of demographic and medical variables on the mediating factors | | | | | | | | | | |
| Morbidity | | | | | | | | | | |
| Current health complaints | 0.00 | **0.23** | –0.01 | –0.11 | **0.23** | 0.06 | **0.28** | –0.03 | –0.01 | –0.02 |
| Physical late effects | 0.03 | 0.08 | 0.00 | **0.27** | 0.17 | –0.02 | –0.09 | 0.09 | **–0.25** | 0.07 |
| Psych/cogn/neur late effects | –0.04 | 0.08 | **0.17** | **–0.16** | 0.18 | 0.09 | 0.00 | –0.08 | –0.05 | –0.03 |
| Course of life | | | | | | | | | | |
| Develop. milestones | –0.01 | –0.02 | **–0.13** | 0.01 | **–0.34** | **–0.20** | –0.13 | 0.01 | –0.12 | 0.06 |
| Risk behaviour | 0.04 | **–0.24** | **–0.13** | **–0.08** | –0.18 | –0.12 | –0.12 | –0.07 | –0.13 | –0.01 |
| Disease-related coping | | | | | | | | | | |
| Interpretative control | 0.05 | **0.19** | 0.05 | –0.05 | 0.01 | 0.07 | 0.02 | –0.04 | –0.01 | –0.09 |
| Vicarious control | 0.06 | –0.04 | –0.10 | –0.06 | –0.10 | –0.03 | –0.02 | –0.07 | –0.04 | –0.09 |
| Predictive control | –0.07 | **–0.16** | –0.05 | 0.01 | **–0.26** | –0.08 | –0.09 | –0.04 | 0.10 | –0.02 |
| Generic coping | | | | | | | | | | |
| Passive coping | –0.05 | **0.23** | 0.12 | **0.22** | 0.00 | –0.07 | –0.04 | **0.21** | **0.15** | –0.04 |
| Active coping | 0.11 | –0.07 | –0.02 | 0.01 | **–0.25** | –0.09 | –0.04 | 0.00 | 0.01 | 0.11 |
| Sharing emotions | 0.08 | **0.23** | 0.04 | –0.06 | –0.19 | –0.01 | –0.12 | 0.01 | 0.07 | 0.03 |
| Social support | –0.03 | **0.17** | 0.04 | **0.17** | –0.04 | 0.02 | 0.10 | 0.01 | 0.13 | 0.02 |
| 2 Effects of demographic variables and relapse/second tumour on HRQoL | | | | | | | | | | |
| Mental functioning (MCS) | –0.05 | –0.08 | | | | | | | | 0.02 |
| Physical functioning (PCS) | –0.08 | **–0.11** | | | | | | | | **–0.08** |

| | Current health complaints | Physical late effects | Psych/cogn/neur late effects | Develop-mental milestones | Risk behaviour | Interpret control | Vicarious control | Predictive control | Passive coping | Active coping | Sharing emotions | Social support | Explained variance§ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 Effects of mediating factors on HRQoL | | | | | | | | | | | | | |
| MCS | **–0.12** | 0.01 | **–0.11** | –0.07 | –0.08 | –0.07 | –0.03 | **0.25** | **–0.29** | **0.21** | **–0.17** | 0.07 | *0.46* |
| PCS | **–0.28** | –0.03 | **–0.15** | 0.04 | –0.06 | **–0.13** | 0.05 | **0.18** | **–0.17** | 0.07 | –0.01 | 0.00 | *0.40* |

*$n = 353$, overall goodness of fit chi-square(14) = 21.61, $P = 0.087$, root mean square error of approximation = 0.039, 90% confidence interval [0.0; 0.070]. Bold regression coefficients differ significantly from zero at $\alpha = 0.05$.
†'Leukaemia/lymhoma' is reference. The variables were dichotomized as follows: brain tumour 1 vs. leukaemia/lymphoma 0; solid tumour 1 vs. leukaemia/lymphoma 0.
‡'Surgery only' is reference. The variables were dichotomized as follows: radiotherapy and chemotherapy with or without surgery 1 vs. surgery only 0; radiotherapy with or without surgery 1 vs. surgery only 0; chemotherapy with or without surgery 1 vs. surgery only 0.
§The model explains 46% and 40% of the variance of MCS and PCS respectively.

*Effects of the mediating factors*

The significant effects of the mediating factors on HRQoL were small to medium, ranging from $\beta = -0.11$ (psychosocial/cognitive/neurological late effects) to $\beta = -0.29$ (passive coping).

Survivors with current health complaints or psychosocial/cognitive/neurological late effects reported worse HRQoL, mentally but especially physically. Both disease-related and generic coping affected HRQoL. The disease-related coping strategies 'interpretative control' affected PCS negatively, while the effect of 'predictive control' on MCS and PCS was positive. The generic coping style 'passive coping' was associated negatively with MCS and PCS, as 'sharing emotions' was with MCS. On the contrary, 'active coping' had a positive effect on MCS. No effects were found of the mediating factors 'physical late effects', 'developmental milestones', 'risk behaviour', 'vicarious control' and 'social support'.

## DISCUSSION

The final and modified model of adjustment to childhood cancer fitted the data closely and explained a substantial part of the variance of HRQoL of the survivors of childhood cancer (Fig. 2, Table 2). The final model was somewhat different from our conceptual model (Fig. 1). It seemed reasonable – data-driven as well as theoretically – to differentiate between characteristics of disease and treatment, and the late medical consequences. Diagnosis and treatment appeared to affect HRQoL via 'current health complaints' and 'psychosocial/cognitive/neurological late effects', so that these variables were considered mediating factors instead of background characteristics. The paths in the model (Table 2) also showed that the medical and demographic characteristics were mediated by generic and disease-related coping. Course of life and social support had no significant (mediating) effects on HRQoL.

Gender is the factor that most frequently affected the mediating factors. In addition, a direct effect of gender on physical HRQoL was found. Female survivors reported more health complaints and worse HRQoL than male survivors, which finding has been reported frequently in previous research (Aaronson *et al.* 1998). Furthermore, female survivors reported less risk behaviour, which means that substance use and antisocial behaviour was more prevalent among male survivors. This gender effect is also known among the general population (Stam *et al.* 2005). Apart from that, it is known that male as well as female survivors reported less risk behaviour than their peers from the general Dutch population (Stam *et al.* 2005). The relation we found between gender and generic coping indicates that men and women have different styles of coping with general life stressors. Female survivors reported more passive coping, were more inclined to share emotions with others and reported more social support than male survivors. These gender differences are in accordance with the results of several studies on generic coping in the general Dutch population (Schreurs *et al.* 1993). Gender effects were also found with respect to disease-related coping. Female survivors searched more for information about their disease (interpretative control), while men were more optimistic about the further course of their disease (predictive control).

Diagnosis and treatment were the medical characteristics that affected the mediating factors most strongly. Survivors having been treated with chemotherapy (with or without radiotherapy) were most at risk of health complaints, while survivors of a brain tumour were most at risk of psychosocial, cognitive or neurological late effects. In turn, these consequences of childhood cancer had a negative impact on both mental and physical functioning in young adulthood.

Survivors of a brain tumour and/or having been treated with radiotherapy had achieved fewer developmental milestones, and the survivors of a brain tumour reported also less risk behaviour. Remarkably, these course-of-life factors exerted no influence on survivors' HRQoL in contrast with previous results (Grootenhuis *et al.* 2006; Maurice-Stam *et al.* 2007). Several explanations could be given. First, coping was not included as predictor of HRQoL in the previous studies. In the present study, coping strategies were revealed to be stronger predictors of HRQoL than the course of life, and coping and course of life were interrelated. Furthermore, we should realize that the instrument used, the RAND-36, measures generic HRQoL generally. Specific questionnaires are needed to measure HRQoL of survivors more thoroughly. In addition, there are other important aspects of the well-being and functioning of survivors, such as educational achievement and marital status, which could be affected by the course of life. Although the mediating effect of the course of life on HRQoL was not been confirmed by our data, the achievement of developmental milestones while growing up is of great importance to adjustment in adult life (Garber 1984; Lewis & Miller 1990; Grootenhuis *et al.* 2006).

Several medical variables affect coping. The results suggest that if the cancer was intrusive – indicated by 'older age at diagnosis', 'longer duration of treatment', 'radiotherapy and chemotherapy' and 'solid tumour' – patients were more inclined to a passive, avoidant coping style, and to less active and predictive strategies.

However, we did not measure coping during treatment so we do not know whether the coping strategies during treatment were the same as found in the present study.

Coping mediated the effects of the background characteristics on HRQoL. Survivors who searched more for information about their disease (interpretative control) reported worse HRQoL as did the survivors who had a passive reaction pattern and shared their emotions with others. On the contrary, an active, problem-focused coping style had a positive impact on HRQoL, which was also true for being optimistic about the further course of the disease (predictive control). In other words, goal-orientated survivors who faced the situation calmly (active problem-focusing) reported better emotional functioning than survivors who coped with stress by taking a passive standpoint and allowing themselves to be totally immersed in the problem (passive reaction pattern). These correlates are not surprising, since passive coping is related to the concept of 'learned helplessness' and active coping to feelings of control over events (Lindahl Norberg *et al.* 2005). The results in the present study were in line with results in other studies about coping with general life stressors and about coping in disease-related situations (Grootenhuis *et al.* 1996; van der Zaag-Loonen *et al.* 2003).

In summary, we conclude that our model explained the process of adjustment to childhood cancer reasonably well, as well as HRQoL as final outcome. Nevertheless, the explained variances in the model can probably be increased by adding factors and outcomes that are found to be relevant in studies on adjustment to paediatric chronic physical disorders (Wallander & Varni 1998; Hartman *et al.* 2004; Raina *et al.* 2004; Raina *et al.* 2005). First, intrapersonal factors such as personality and temperament may affect adjustment (Wallander & Varni 1998). However, personality and temperament characteristics were expressed partly in the personal coping styles measured in our study. Second, social–ecological factors were not included in our model, such as family functioning and socio-economic factors. Third, the concepts 'self-esteem' and 'mastery' could be predictive of adjustment (Hartman *et al.* 2004; Raina *et al.* 2005). Finally, the present study focused on HRQoL outcomes; however, there are of course other interesting aspects indicative of patients' (mal)adjustment, e.g. post-traumatic stress symptoms (Kazak 1998; Hobbie *et al.* 2000; Meeske *et al.* 2001; Langeveld *et al.* 2004a; Schwartz & Drotar 2006) and socio-economic outcomes (Langeveld *et al.* 2003; Nagarajan *et al.* 2003; Pui *et al.* 2003).

After all, one should realize that, overall, most survivors appear to cope well with the cancer experience and the late consequences of the disease and its treatment. Insight into the factors that affect HRQoL may alert clinicians to patients vulnerable to psychosocial problems. The model shows us that survivors having been treated with chemotherapy and radiotherapy are most at risk for worse HRQoL, because they suffer more from current health complaints and were less inclined to predictive and active coping. The model shows that it could be useful to give attention to survivors' way of coping with their disease and with general life stressors, because some coping strategies appeared to be more helpful than others.

By examining the entire model, the importance of monitoring survivors medically as well as psychosocially was stressed. In some hospitals, survivors are screened psychosocially by a psychologist during the annual evaluation at the long-term follow-up clinic. It would be useful to discuss coping strategies, especially if problems were reported. Giving attention to the achievement of developmental milestones is also recommended because several medical variables appeared to influence the achievement of the milestones unfavourably. Increasingly, computer-scored individual measurement of HRQoL is used in clinical practice, in order to inform the physician about the patient's HRQoL (Detmar & Aaronson 1998; Detmar *et al.* 2002; Nagarajan *et al.* 2003; Velikova *et al.* 2004; Varni *et al.* 2005). The computer output – usually a graphical summary of HRQoL outcomes – assists the physician to focus at the HRQoL domains that correspond with patients needs. Utilizing HRQoL measurement can facilitate patient–physician communication and identification of patients with the greatest needs (Detmar & Aaronson 1998; Varni *et al.* 2005), so that referring to other health care providers is possible.

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## REFERENCES

Aaronson N.K., Muller M., Cohen P.D.A., Essink-Bot M., Fekkes M., Sanderman R., Sprangers M.A.G., te Velde A. & Verrips E. (1998) Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *Journal of Clinical Epidemiology* **51**, 1055–1068.

Bollen K.A. (1989) *Structural Equations with Latent Variables*. Wiley, New York, USA.

Browne M.W. & Cudeck R. (1992) Alternative ways of assessing model fit. *Sociological Methods Research* **21**, 230–258.

Cohen J. (1988) *Statistical Power Analysis for the Behavioral Sciences*. Academy Press, New York, USA.

Detmar S.M. & Aaronson N.K. (1998) Quality of life assessment in daily clinical oncology practice: a feasibility study. *European Journal of Cancer* **34**, 1181–1186.

Detmar S.B., Muller M.J., Schornagel J.H., Wever L.D.V. & Aaronson N.K. (2002) Health-related quality-of-life assessment and patient–physician communication. A randomized controlled trial. *JAMA* **288**, 3027–3034.

Doeglas D., Suurmeijer T., Briancon S., Moum T., Krol B., Bjelle A., Sanderman R. & Van den Heuvel W. (1996) An international study on measuring social support: interactions and satisfaction. *Social Science and Medicine* **43**, 1389–1397.

Eiser C. (2004) *Children with Cancer: The Quality of Life.* Lawrence Erlbaum Associates Publishers, Mahwah, NJ, USA.

Fritz G.K., Williams J.R. & Amylon M. (1988) After treatment ends: psychosocial sequelae in pediatric cancer survivors. *American Journal of Orthopsychiatry* **58**, 552–561.

Garber J. (1984) Classification of childhood psychopathology: a developmental perspective. *Child Development* **55**, 30–48.

Grootenhuis M.A. & Last B.F. (2001) Children with cancer with different survival perspectives: defensiveness, control strategies, and psychological adjustment. *Psycho-Oncology* **10**, 305–314.

Grootenhuis M.A., Last B.F., de Graaf-Nijkerk J.H. & van der Wel M. (1996) Secondary control strategies used by parents of children with cancer. *Psycho-Oncology* **5**, 91–102.

Grootenhuis M.A., Stam H., Destrée-Vonk A., Heijmans H.S.A. & Last B.F. (2003) Levensloop Vragenlijst voor Jong-Volwassenen [Course of life questionnaire for young adults]. *Gedrag and Gezondheid* **31**, 336–350.

Grootenhuis M.A., Stam H., Last B.F. & Groothoff J.W. (2006) The impact of delayed development on the quality of life of adults with end-stage renal disease since childhood. *Pediatric Nephrology* **21**, 538–544.

Hartman E.E., Oort F.J., Aronson D.C., Hannekam M.J.G., van der Zee D.C., Rieu P.N.M.A., Madern G.C., De Langen Z.J., van Heurn L.W.E., van Silfhout-Bezemer M., Looyaart N. & Sprangers M.A.G. (2004) Critical factors affecting quality of life of adult patients with anorectal malformations or Hirschsprung's disease. *American Journal of Gastroenterology* **99**, 907–913.

Hobbie W.L., Stuber M., Meeske K., Wissler K., Rourke M.T., Ruccione K., Hinkle A. & Kazak A. (2000) Symptoms of posttraumatic stress in young adult survivors of childhood cancer. *Journal of Clinical Oncology* **18**, 4060–4066.

Houtzager B.A., Oort F.J., Hoekstra-Weebers J.E.H.M., Caron H.N., Grootenhuis M.A. & Last B.F. (2004) Coping and family functioning predict longitudinal psychological adaptation of siblings of childhood cancer patients. *Journal of Pediatric Psychology* **29**, 591–605.

Jöreskog K.G. & Sörbom D. (1996) *LISREL 8 User's Guide*. Scientific Software International, INC, Chicago, IL, USA.

Kazak A.E. (1998) Posttraumatic distress in childhood cancer survivors and their parents. *Medical and Pediatric Oncology Supplement* **1**, 60–68.

Kazak A.E., Barakat L.P., Meeske K., Christakis D., Meadows A.T., Penati B. & Stuber M.L. (1997) Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. *Journal of Consulting and Clinical Psychology* **65**, 120–129.

Langeveld N.E., Stam H., Grootenhuis M.A. & Last B.F. (2002) Quality of life in young adult survivors of childhood cancer (review). *Supportive Care in Cancer* **10**, 579–600.

Langeveld N.E., Ubbink M.C., Last B.F., Grootenhuis M.A., Voûte P.A. & de Haan R.J. (2003) Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. *Psycho-Oncology* **12**, 213–225.

Langeveld N.E., Grootenhuis M.A., Voûte P.A. & de Haan R.J. (2004a) Posttraumatic stress symptoms in adult survivors of childhood cancer. *Pediatric Blood Cancer* **42**, 604–610.

Langeveld N.E., Grootenhuis M.A., Voûte P.A., de Haan R.J. & van den Bos C. (2004b) Quality of life, self-esteem and worries in young adult survivors of childhood cancer. *Psycho-Oncology* **13**, 867–881.

Last B.F., Grootenhuis M.A., Destrée-Vonk A. & Heymans H.S.A. (2000) De ontwikkeling van een levensloopvragenlijst voor jong-volwassenen (LVJV) [Development of a course of life questionnaire for young adults]. *Gedrag and Gezondheid* **8**, 22–30.

Lewis M. & Miller S.M. (1990) *Handbook of Developmental Psychopathology*. Plenum Press, New York, USA.

Lindahl Norberg A., Lindblad F. & Boman K.K. (2005) Coping strategies in parents of children with cancer. *Social Science and Medicine* **60**, 965–975.

Loonen H.J., Grootenhuis M.A., Last B.F., Koopman H.M. & Derkx H.H.F. (2002) Quality of life in peadiatric inflammatory bowel disease measured by a generic and disease-specific questionnaire. *Acta Paediatrica* **91**, 341–354.

Magnani C., Pastore G., Coebergh J., Viscomi S., Spix C. & Steliarova-Foucher E. (2006) Trends in survival after childhood cancer in Europe, 1978–1997: report from the Automated Childhood Cancer Information system project (AGGIS). *European Journal of Cancer* **42**, 1981–2005.

Maurice-Stam H., Grootenhuis M.A., Caron H.N. & Last B.F. (2007) Course of life of survivors of childhood cancer is related to quality of life in young adulthood. *Journal of Psychosocial Oncology* **25**, 43–58.

Meeske K.A., Ruccione K., Globe D.R. & Stuber M.L. (2001) Posttraumatic stress, quality of life, and psychological distress in young adult survivors of childhood cancer. *Oncology Nursing Forum* **28**, 481–489.

Nagarajan R., Nelgia J.P., Clohisy D.R., Yasui Y., Greenberg M., Hudson M., Zevon M.A., Tersak J.M., Ablin A. & Robison L.L. (2003) Education, employment, insurance, and marital status among 694 survivors of pediatric lower extremity bone tumours. *Cancer* **97**, 2554–2564.

Novakovic B. (1994) U.S. Childhood cancer survival, 1973–1987. *Medical and Pediatric Oncology* **23**, 480–486.

Oldehinkel A.J., Koeter M.W.J., Ormel J. & Van den Brink W. (1992) Omgaan met problematische situaties [Coping with problematic situations]. *Gedrag & Gezondheid* **20**, 236–244.

Paulides J., Kamps W.A. & Caron H. (2000) *Childhood Cancer in the Netherlands, 1989–1997*. Association of Comprehensive Cancer Centres, Utrecht, the Netherlands.

Phipps S. & Srivastava D.K. (1997) Repressive adaptation in children with cancer. *Health Psychology* **16**, 521–528.

Phipps S., Larson S., Long A. & Rai S.N. (2006) Adaptive style and symptoms of posttraumatic stress in children with cancer and their parents. *Journal of Pediatric Psychology* **30**, 1–12.

Pui C.-H., Cheng C., Leung W., Rai S.N., Rivera G.K., Sandlund J.T., Ribeiro R.C., Relling M.V., Kun L.E., Evans W.E. & Hudson M.M. (2003) Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. *The New England Journal of Medicine* **349**, 640–649.

Raina P., O'Donnell M., Schwellnus H., Rosenbaum P., King G., Brehaut J., Russel D., Swinton M., King S., Wong M., Walter S.D. & Wood E. (2004) Caregiving process and caregiver burden: conceptual models to guide research and practice. *BMC Pediatrics* **4**, 1–13.

Raina P., O'Donnell M., Rosenbaum P., Brehaut J., Walter S.D., Russell D., Swinton B., Zhu B. & Wood E. (2005) The health and well-being of caregivers of children with cerebral palsy. *Pediatrics* **115**, e626–e636.

Rothbaum F., Weisz J.R. & Snyder S.S. (1982) Changing the world and changing the self: a two-process model of perceived control. *Journal of Personality and Social Psychology* **42**, 5–37.

Sankila R., Martos Jiménez M.C., Miljus D., Pritchard-Jones K., Steliarova-Foucher E. & Stiller C. (2006) Geographical comparison of cancer survival in european children (1988–1997). Report from the Automated Childhood Cancer Information System project European. *Journal of Cancer* **13**, 1980.

Schreurs P.J., Willige G., Brosschot J.F., Tellegen B. & Graus G.M.H. (1993) *De Utrechtse Coping Lijst: UCL herziene handleiding [The Utrecht Coping List: UCL-Manual]*. Swets & Zeitlinger, Lisse, the Netherlands.

Schwartz L. & Drotar D. (2006) Posttraumatic stress and related impairment in survivors of childhood cancer in early adulthood compared to healthy peers. *Journal of Pediatric Psychology* **31**, 356–366.

Sloper T., Larcombe I.J. & Charlton A. (1994) Psychosocial adjustment of five-year survivors of childhood cancer. *Journal of Cancer Education* **9**, 163–169.

van Sonderen E. (2004) *Het Meten Van Sociale Steun Met de Sociale Steun Lijst-Interacties (SSL-I) En Sociale Seun Lijst Discrepanties (SSL-D): Een Handleiding [Measurement of Social Support with the Social Support Questionnaire – Interactions and the Social Support Questionnaire – Discrepancies: Manual] Noordelijk Centrum Voor Gezondheidsvraagstukken*. Rijksuniversiteit Groningen, Groningen, the Netherlands.

SPSS (2002) *SPSS 11.5 Syntax Reference Guide: Base System, Advanced Models, Regression Models*. SPSS Inc, Chicago, IL, USA.

Stam H., Grootenhuis M.A. & Last B.F. (2001) Social and emotional adjustment in young survivors of childhood cancer (review). *Supportive Care in Cancer* **9**, 489–513.

Stam H., Grootenhuis M.A. & Last B.F. (2005) The course of life of survivors of childhood cancer. *Psycho-Oncology* **14**, 227–238.

Stam H., Grootenhuis M.A. & Last B.F. (2006) Quality of life and coping in young adult survivors of childhood cancer: positive expectations about the further course of the disease were correlated with better quality of life. *Psycho-Oncology* **15**, 31–43.

Stevens M.C.G., Mahler H. & Parkes S. (1998) The health status of adult survivors of cancer in childhood. *European Journal of Cancer* **34**, 694–698.

Stiller C.A. & Draper G.J. (1998) The epidemiology of cancer in children. In: *Cancer in Children: Clinical Management*, 4th edn. (eds Voûte P.A., Kalifa C. & Barrett A.), pp. 9–20. Oxford University Press, Oxford, UK.

Stiller C.A. & Draper G.J. (2005) The epidemiology of cancer in children. In: *Cancer in Children: Clinical Management*, 5th edn. (eds Voûte P.A. *et al.*), pp. 1–16. Oxford University Press, Oxford, USA.

Suurmeijer Th.P.B.M., Doeglas D.M., Briancon S., Krijnen W., Krol B., Sanderman R., Moum T., Bjelle A. & Van den Heuvel W.J.A. (1995) The measurement of social support in the 'European research on incapacitating disease and social support': the development of the Social Support Questionnaire for Transactions (SSQT). *Social Science and Medicine* **40**, 1221–1229.

Varni J.W., Burwinkle T.M. & Lane M.M. (2005) Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application. *Health and Quality of Life Outcomes* **3**, 1–9.

Velikova G., Booth L., Smith A.B., Brown P.M., Lynch P., Brown J.M. & Selby P.J. (2004) Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *Journal of Clinical Oncology* **22**, 714–724.

Wallander J.L. & Varni J.W. (1998) Effects of pediatric chronic physical disorders on child and family adjustment. *Journal of Child Psychology and Psychiatry* **39**, 29–46.

Ware J.E. & Kosinski M. (2001) Interpreting SF-36 summary health measures: a response. *Quality of Life Research* **10**, 405–413.

Wilson I.B. & Cleary P.D. (1995) Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. *Journal of American Medical Association* **273**, 59–65.

van der Zaag-Loonen H.J., Grootenhuis M.A., Last B.F. & Derkx H.H.F. (2003) Coping strategies and quality of life of adolescents with inflammatory bowel disease. *Quality of Life Research* **13**, 1011–1019.

Zebrack B.J. & Chesler M.A. (2002) Quality of life in childhood cancer survivors. *Psycho-Oncology* **11**, 132–141.

Zebrack B.J., Zeltzer L.K., Whitton J., Mertens A.C., Odom L., Berkow R. & Robison L.L. (2002) Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and Non-Hodgkin's lymphoma: a report from the childhood cancer survivor study. *Pediatrics* **110**, 42–52.

Zebrack B.J., Gurney J.G., Oeffinger K., Whitton J., Packer R.J., Mertens A., Turk N., Castleberry R., Dreyer Z.A., Robison L.L. & Zeltzer L.K. (2004) Psychological outcomes in long-term survivors of childhood brain cancer: a report from the Childhood Cancer Survivors Study. *Journal of Clinical Oncology* **22**, 999–1006.

van der Zee K.I. & Sanderman R. (2003) *Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding. [Measuring general health status with the RAND-36. A guide.] Noordelijk Centrum voor Gezondheidsvraagstukken*. Rijksuniversiteit Groningen, Groningen, the Netherlands.